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(54) Title: NANOSHELL THERAPY

(57) Abstract: Nano-constructs comprising nanoshells and methods of using the nano-constructs for treating or ameliorating a vascular condition are provided.

NANOSHELL THERAPY

Field of the Invention

This invention is generally related to using nanoshells for treating or ameliorating a vascular condition such as atherosclerotic plaque.

Description of the State of the Art

Stents are used not only as a mechanical intervention of vascular conditions but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents which have been applied in PTCA procedures include stents illustrated in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

One strategy of biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. However, in many patients, especially diabetic patients, stentable lesions are focal manifestations of widespread vascular disease. The advent of drug eluting stents has brought relief from restenosis of the treated lesion, but leaves progression of regional vascular disease unaddressed. Moreover, drug related therapies sometimes can lead to undesirable side effects.

The embodiments described below address the above-identified problems.

SUMMARY

The present invention provides methods for treating or ameliorating vascular conditions using nano-constructs that include nanoshells. The nanoconstructs can be delivered to a target tissue such as a diseased tissue in a subject by any mode of delivery, e.g., injection. Upon delivery, the nano-constructs can reach the target site via passive targeting or active targeting. Energy can then be applied to the nano-constructs. Upon exposure to energy, the nano-constructs can absorb the energy and translate the energy into heat, thereby ablating the diseased tissue.

In some embodiments, it is provided a method of treating or ameliorating a vascular condition, the method including:

(a) administering to a subject nano-constructs capable of absorbing energy from an electromagnetic radiation or energy from a fluctuating electromagnetic field and translating the energy into heat,

(b) causing the nano-constructs to reach a target tissue, and

(c) applying an energy to the nano-constructs to cause the nano-constructs to heat the target tissue,

wherein the nano-construct comprises a nanoshell.

In some embodiments, it is provided a medical device for treating or ameliorating a vascular condition, the device including:

(a) nano-constructs that comprises nanoshells, and

(b) delivery means for delivering the nano-construct to a target tissue of a subject,

wherein the nanoshells are capable of absorbing an energy from an electromagnetic radiation or energy from a fluctuating electromagnetic field and translating the energy into heat.

Examples of the vascular condition that can be treated or ameliorated by the method described herein include, but are not limited to, atherosclerotic plaque.

DETAILED DESCRIPTION

The present invention provides nano-constructs for treating or ameliorating a vascular condition. The nano-constructs include nanoshells capable of capable of absorbing energy from an electromagnetic radiation or energy from a fluctuating electromagnetic field and translating the energy into heat.

The nano-constructs described herein have nanoshells formed on a core material. The nanoshells include a metal, carbon, or a conducting polymer. The nano-constructs can be administered to a target tissue of a subject, which can be human or an animal. An energy source can then be applied to the nano-constructs. The nano-constructs absorb the energy and then translate the energy into heat, thereby providing therapy to the subject.

The nano-constructs can be used to treat or to ameliorate a vascular condition such as atherosclerotic plaque. Other vascular conditions that can be treated or ameliorated the vascular condition include, but are not limited to, vulnerable plaque, vascular inflammation, diffuse atherosclerotic disease, or restenosis.

In some embodiments, the nanoshells include a metal or an alloy. Useful metals include gold or gold alloy. In some embodiments, the metal or metal alloy can include silver, platinum, palladium, chromium, iridium, biodegradable metals such as magnesium, zinc, calcium, or tungsten, or alloys thereof.

In some embodiments, the nanoshells include carbon. In some embodiments, the nanoshells can have a conducting polymer. Conducting polymers can be, for example, poly(pyrrole), poly(thiophene), poly(acetylene), poly(aniline), graphite, carbon nanotubes, DNA or combinations thereof.

The nanoshells have a thickness in the range between about 2 nm and about 100 nm. Thickness of the shells and the ratio of core to shell dimension is relevant to the frequency of electromagnetic radiation or irradiation that the shells can absorb and translate into heat.

For example, for nanoshells formed of a metal such as gold, the wavelength at which extinction efficiency is maximal shifts to longer wavelength as core to shell ratio increases, i.e. as shell thickness decreases if the outer diameter is kept constant. Most relevant, the nanoshells can be designed such that they absorb radiation energy in the near-infrared spectrum between 650nm and 900nm which is permeable for tissue (see, e.g., Oldeburg S.J., et al., Applied Physics Letters; Vol. 75(19): 2897-2899; Oldenburg S.J., et al., Chemical Physics Letters 288:243-247 (1998)).

The nanoshells can be formed on a non-conducting core material that can include, for example, silicon oxide, silica, aluminum oxide, biopolymers, a polymer, or a combination of these.

The nano-constructs described herein can be delivered to a subject for treating or ameliorating a vascular condition such as atherosclerotic plaque. Upon delivery, the nano-constructs can reach the target site via passive targeting or active targeting. Passive targeting can be achieved by extravasation of the nano-construct through leaky vasculature such as those present in atherosclerotic plaque. In some embodiments, the result of passive targeting can be assessed by the time span after delivery of the nano-constructs and the circulation time of the nano-constructs after delivery. Generally, the longer the nano-constructs remain in circulation, the more the nano-constructs can reach the target site or target tissue, which sometimes is also referred to as the diseased site or diseased tissue. Therefore, in some embodiments, passive targeting can be enhanced by increasing circulation times by rendering the surface of the nano-construct stealthy using a compound such as poly(ethylene glycol). Other compounds that can be used to stealth the nano-constructs include, but are not limited to, hyaluronic acid, phosphoryl choline, dextran, dextrose, sulfo betaine, polypyrrolidone, poly(2-hydroxyethyl methacrylate), albumin, poly(acrylic acid), and poly(methacrylic acid) and PVA.

Extravasation of the nano-constructs is also related to the position and nature of the diseased tissue. The capillary walls of tumor vasculature and the inflamed vasculature of diseased tissue is leaky compared to normal tissue. In some embodiments, extravasation can be achieved by circulation of the nano-constructs in the blood stream for a period ranging from 10 minutes to 120 hours, more specifically ranging from about 4 hours to 48 hours.

In some embodiments, the targeting can be achieved by active targeting. Active targeting can be carried out by attaching a targeting molecule on the nano-constructs (e.g., nanoshells). Targeting molecules include any peptide, antibody, or polysaccharide that has affinity to the target tissue or target site (e.g., atherosclerotic plaque). In some embodiments, the targeting molecule can be a surface-conjugated ligand against a receptor on an inflamed endothelium. Some examples of the targeting molecules are antibodies to CD34, RGD, YIGSR, peptides and antibodies to IIbIIIa, heparin, hyaluronic acid, laminin, collagen, ICAM-1, ICAM-2, ICAM-3, fibrinogen, fibronectin, vitronectin, thrombospondin, osteopontin, integrins, VCAM-1, N-CAM, PECAM-1, IgCAM, folate, oligonucleotide aptamers, selectins, and cadherins.

The result of active targeting can be assessed by measuring the quantity of nano-constructs in the targeted tissue (i.e. vessel wall) versus the quantity administered. Similar to passive targeting, in some embodiments, the result of active targeting can be assessed by the time span after delivery of the nano-constructs and the circulation time of the nano-constructs after delivery. Generally, the longer the nano-constructs remain in circulation, the more the nano-constructs can reach the target site. Therefore, in some embodiments, active targeting mediated by a targeting moiety can be enhanced by increasing circulation times by stealthing the surface of the nano-construct using a compound such as poly(ethylene glycol). Other compounds that can be used to stealth the nano-constructs

include, but are not limited to, hyaluronic acid, phosphoryl choline, dextran, dextrose, sulfo betaine, poly(vinyl alcohol) (PVOH), polypyrrolidone, poly(2-hydroxyethyl methacrylate), albumin, poly(acrylic acid), and poly(methacrylic acid) and PVA.

Active targeting of the nano-constructs is also related to the position and nature of the diseased tissue. Nano-constructs can reach diseased tissue, which is highly vascularized, by systemic administration. Diseased tissue protected by the blood-brain barrier, which can prevent penetration of the nano-constructs, could be more advantageously accessed by administration into cerebro-spinal fluid. If a high concentration of nano-constructs is desired in the vessel wall of a portion of the vascular system, then administration by local delivery catheter may be employed. Some target tissues such as the eye or prostate can be accessed externally by direct injection. In some embodiments, active targeting can be achieved by circulation of the nano-constructs in the blood stream for a period ranging from 10 minutes to 120 hours, more specifically ranging from about 4 hours to 48 hours.

Methods of forming nanoshells

Nanoshells can be formed on a core material using established methods. For example, U.S. Patent No. 6,699,724 describes forming conducting nanoshells on a non-conducting core. The size and thickness of the core/shell can be tuned so that the particles can absorb light with a desired wavelength. Biomolecules such as proteins or peptides can be attached to the nanoshells for binding to a specific tissue.

U.S. Patent No. 6,685,986 describes a method of forming metal nanoshells upon a core substrate. The nanoshells can be formed of a metal such as gold or a conducting polymer. The core substrate can be particles of silicon dioxide, titanium dioxide, alumina, zirconia, poly(methyl methacrylate) (PMMA), polystyrene, gold sulfide, macromolecules such as dendrimers, semiconductors such as CdSe, CdS, or GaAs. The particles can

further have polyvinyl alcohol (PVA), latex, nylon, Teflon, acrylic, Kevlar, epoxy, or glasses. Some other references, for example, U.S. application publication Nos. 2003/0164064, 2002/0061363, 2002/0187347, 2002/0132045, and 2005/0056118, also describes various methods of forming metal nanoshells on a core substrate. Formation of partial nanoshells can be formed according to the method described in, for example, U.S. Patent No. 6,660,381.

In some embodiments, the nanoshells can be formed via metal colloidal nanoparticles such as colloidal gold nanoparticles. For example, colloidal gold nanoparticles of 3-4 nm size can assemble on nanoparticle surfaces functionalized by amine groups. These nanoparticles act as nucleation sites, and when a gold salt is present in a reducing environment, a solid gold shell can be formed around a nanosize template such as a nanosphere.

In some embodiments, polymeric nanoparticles such as commercially available polystyrene particles modified at their surface to present amine groups may be used as a template for gold nanoshells. Amine functionality can be placed onto these polymers by a variety of techniques. For example, polymeric surface can be modified to have amine functionality via plasma treatment in the presence of ammonia or hydrazine. This plasma process can be carried out on preformed nanoparticles by agitating them in a plasma reactor. Amino groups can also be incorporated into the end-groups of a polymer (e.g., a biodegradable polymer), if the initiator contains both a hydroxyl group and an amino group protected by a carbobenzoxy group or a t-butoxycarbonyl group, and this initiator is used to make a biodegradable polymer by ring opening polymerization, such as poly(L-lactide) or polyglycolide. After the polymerization, the protecting group can be removed, liberating the amino group. Polymeric methacrylates canbe made with amino groups by using a monomer such as N-(3-aminopropyl)methacrylamide. A copolymer with other

monomers such has butyl methacrylate or methyl methacrylate can be made. In some embodiments, a dispersion or emulsion polymerization process can be used to form monodisperse nanoparticles with surface amino groups (see, e.g., Ramos;Jose, Forcada; Jacqueline . Polymer 47(4):1405 (2006); Ramos;Jose, Forcada; Jacqueline, Polymer Chemistry 43 (17):3878 (2005); Prakash, G.K. et al., J. of Nanoscience and Nanotechnology 5(3):397 (2005); and Musyanovych, Anna; Adler, Hans-Jurgen Organic Chemistry III Macromolecular Society, 21(6):2209 (2005).

In some embodiments, the nanoshells can be formed via thiol group facilitated nanoparticle assembling. For example, biodegradable poly(propylene sulfide) can be produced in nanoparticle form as shown by Annemie Rehor (Ph.D. thesis, Swiss Federal Institute of Technology, Zurich, 2005). This polymer has thiol end-groups from the polymerization, which can be maximized in number by exposing the nanoparticles to reducing conditions.

In some embodiments, the nanoshells can be modified to include a targeting molecule. The target molecule can be any peptides or antibodies such as ligands against receptors on an inflamed endothelium. Examples of such targeting molecules include, but are not limited to, antibodies to CD34, RGD, YIGSR, peptides and antibodies to IIbIIIa, heparin, hyaluronic acid, laminin, collagen, ICAM-1, ICAM-2, ICAM-3, fibrinogen, fibronectin, vitronectin, thrombospondin, osteopontin, integrins, VCAM-1, N-CAM, PECAM-1, IgCAM, folate, oligonucleotide aptamers, selectins, and cadherins.

Attachment of targeting molecule to nanoshells can be achieved by established methods. The targeting molecule can be attached to the nanoshell via covalent bonding or non-covalent conjugation. Non-covalent conjugation can be based on ionic interaction, hydrogen bonding or other type of interaction. For example, after formation of the gold nanoshell, molecules functionalized with a thiol group can be used to modify the nanoshell

surface for targeting of the nanoshell, or to stealth the nanoshell surface. Thiol-terminated molecules have been shown to self-assemble on gold surfaces. For example, thiol-terminated poly(ethylene glycol) (PEG) having a molecular weight of about 200 Daltons to 10,000 Daltons, preferably between 500 Daltons to about 2,000 Daltons can be used to stealth the nanoshell surface. The other end of the PEG chain can be functionalized with a targeting molecule such as a peptide or an antibody to target the nanoshell to specific tissue within the body.

In some embodiments, the targeting molecule can be attached to a nanoshell via a spacer. A spacer molecule can be a short chain alkyl group such as a C1-C20 alkyl, C3-C20 cycloalkyl, poly(ethylene glycol), poly(alkylene oxide). Some other spacer molecules can be, but are not limited to, dextran, dextrose, heparin, poly(propylene sulfide), hyluronic acid, peptides, DNA, PVA and PVP.

Biocompatible polymers

Polymers that can be used as the core substrate for forming the nanoshells described above can be biodegradable (either bioerodable or bioabsorbable or both) or nondegradable, and can be hydrophilic or hydrophobic.

Representative biocompatible polymers include, but are not limited to, poly(ester amide), polyhydroxyalkanoates (PHA), poly(3-hydroxyalkanoates) such as poly(3-hydroxypropanoate), poly(3-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxyhexanoate), poly(3-hydroxyheptanoate) and poly(3-hydroxyoctanoate), poly(4-hydroxyalkanaote) such as poly(4-hydroxybutyrate), poly(4-hydroxyvalerate), poly(4-hydroxyhexanote), poly(4-hydroxyheptanoate), poly(4-hydroxyoctanoate) and copolymers including any of the 3-hydroxyalkanoate or 4-hydroxyalkanoate monomers described herein or blends thereof, poly(D,L-lactide), poly(L-lactide), polyglycolide, poly(D,L-lactide-co-glycolide), poly(L-lactide-co-glycolide), polycaprolactone, poly(lactide-co-

caprolactone), poly(glycolide-co-caprolactone), poly(dioxanone), poly(ortho esters), poly(anhydrides), poly(tyrosine carbonates) and derivatives thereof, poly(tyrosine ester) and derivatives thereof, poly(imino carbonates), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), polycyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyphosphazenes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride, polyvinyl ethers, such as polyvinyl methyl ether, polyvinylidene halides, such as polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate, copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers, polyamides, such as Nylon 66 and polycaprolactam, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, poly(glyceryl sebacate), poly(propylene fumarate), poly(n-butyl methacrylate), poly(sec-butyl methacrylate), poly(isobutyl methacrylate), poly(tert-butyl methacrylate), poly(n-propyl methacrylate), poly(isopropyl methacrylate), poly(ethyl methacrylate), poly(methyl methacrylate), epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, polyethers such as poly(ethylene glycol) (PEG), copoly(ether-esters) (e.g. poly(ethylene oxide-co-lactic acid) (PEO/PLA)), polyalkylene oxides such as poly(ethylene oxide), poly(propylene oxide), poly(ether ester), polyalkylene oxalates, phosphoryl choline, choline, poly(aspirin), polymers and co-polymers of hydroxyl bearing monomers such as 2-hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA), hydroxypropylmethacrylamide, PEG acrylate

(PEGA), PEG methacrylate, 2-methacryloyloxyethylphosphorylcholine (MPC) and *n*-vinyl pyrrolidone (VP), carboxylic acid bearing monomers such as methacrylic acid (MA), acrylic acid (AA), alkoxymethacrylate, alkoxyacrylate, and 3-trimethylsilylpropyl methacrylate (TMSPMA), poly(styrene-isoprene-styrene)-PEG (SIS-PEG), polystyrene-PEG, polyisobutylene-PEG, polycaprolactone-PEG (PCL-PEG), PLA-PEG, poly(methyl methacrylate)-PEG (PMMA-PEG), polydimethylsiloxane-co-PEG (PDMS-PEG), poly(vinylidene fluoride)-PEG (PVDF-PEG), PLURONIC™ surfactants (polypropylene oxide-co-polyethylene glycol), poly(tetramethylene glycol), hydroxy functional poly(vinyl pyrrolidone), biomolecules such as collagen, chitosan, alginate, fibrin, fibrinogen, cellulose, starch, dextran, dextrin, hyaluronic acid, fragments and derivatives of hyaluronic acid, heparin, fragments and derivatives of heparin, glycosamino glycan (GAG), GAG derivatives, polysaccharide, elastin, or combinations thereof. In some embodiments, the nanoparticles can exclude any one of the aforementioned polymers.

As used herein, the terms poly(D,L-lactide), poly(L-lactide), poly(D,L-lactide-co-glycolide), and poly(L-lactide-co-glycolide) can be used interchangeably with the terms poly(D,L-lactic acid), poly(L-lactic acid), poly(D,L-lactic acid-co-glycolic acid), or poly(L-lactic acid-co-glycolic acid), respectively.

Method of Use

The nano-constructs provided herein can be delivered or administered to a subject via any established mode of delivery. For example, the nano-constructs can be delivered by systemic delivery such as systemic injection. In some embodiments, the nano-constructs can be administered by local delivery such as direct injection. For disorders of the vascular system, the nano-constructs may be administered by catheter-based devices. These would include single and dual needle injection catheters, porous balloon catheters, balloon catheters with jets, and double balloon catheters.

Upon delivery to the target tissue, an energy source can be applied to the nano-constructs. The nano-constructs can then absorb the energy and convert it or translate it to heat so as to ablate the diseased tissue. The energy source can be in any form capable of reaching the nano-constructs and being absorbed and converted by the nano-constructs into heat. In some embodiments, the energy source can be applied through external radiation or through a catheter-based guidance system.

In some embodiments, the energy source is an electromagnetic radiation having a wave length ranging from 500 nm to 1500 nm. For example, the energy source can be a near infrared radiation.

In some embodiments, the energy source is a fluctuating electromagnetic field. Such electromagnetic field can have a frequency ranging from 1×10^6 Hz to 6×10^{14} Hz. In some embodiments, the electromagnetic field can have a frequency of 700 nm to 1300 nm where optical transmission is optimal (Welch A.; van Gemert, M. e. *Optical-Thermal Response of Laser Irradiated Tissue*, Plenum Press: New York, 1995).

In some embodiments, the energy source can be applied to the nano-constructs by a catheter-based fiber-optic. The localization of plaque can be imaged prior to the procedure or during the procedure by interrogation with an attenuated radiation. For example, the plaque may be imaged by optical coherence tomography using a wavelength of 1300 nm (Meissner O. A., et al. J Vasc Interv Radiol 2006; 17: 343-349) or intravascular ultrasound (Colombo et al., Circulation, 91:1676-88 (1995)). This same wavelength could then be used to apply energy to the nano-constructs after they are administered.

The nano-construct described herein can be used to treat, prevent or ameliorate a medical condition. Such a medical condition can be, e.g., a tumor or nephropathic kidney. In some embodiments, such a site can be a site of atherosclerosis. Other medical

conditions include, but are not limited to, vulnerable plaque, diffuse atherosclerotic disease, diabetic retinopathy, aneurysm, anastomotic hyperplasia, claudication, chronic total occlusion, dysfunctional endothelium, recurring thrombus, fibrin accumulation, or combinations of these.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

I claim:

1. A method of treating or ameliorating a vascular condition, comprising:

(a) administering to a subject nano-constructs capable of absorbing energy from an electromagnetic radiation or energy from a fluctuating electromagnetic field and translating the energy into heat,

(b) causing the nano-constructs to reach a target tissue, and

(c) applying an energy to the nano-constructs to cause the nano-constructs to heat the target tissue,

wherein the nano-construct comprises a nanoshell.

2. The method of claim 1, wherein the causing comprises allowing the nano-constructs to extravasate through leaky vasculature in the target tissue.

3. The method of claim 1, wherein the nano-constructs comprise targeting molecules on the surface of the nano-constructs.

4. The method of claim 3, wherein the targeting molecules are surface-conjugated ligands against receptors on an inflamed endothelium.

5. The method of claim 1, wherein the energy is a near infrared (NIR) electromagnetic radiation applied through a catheter-based fiber-optic.

6. The method of claim 1, wherein the energy is from electromagnetic irradiation applied outside the body of the subject.

7. The method of claim 2, wherein the nano-constructs comprise a surface-stealthing compound on the surface of the nano-constructs such that the circulation time of the nano-constructs is increased.

8. The method of claim 7, wherein the surface-stealthing compound is poly(ethylene glycol).

9. The method of claim 1, wherein the nanoshell comprises a material selected from a metal, carbon, or a conducting polymer.

10. The method of claim 1, wherein the nanoshell comprises gold.

11. The method of claim 1, wherein the nanoshell has a thickness in the range between about 2 nm and about 100 nm.

12. The method of claim 1, wherein the vascular condition is selected from atherosclerotic plaque, vulnerable plaque, diffuse atherosclerotic disease, diabetic retinopathy, aneurysm, anastomotic hyperplasia, claudication, chronic total occlusion, dysfunctional endothelium, recurring thrombus, fibrin accumulation, or combinations of these.

13. The method of claim 13, wherein the atherosclerotic plaque is located by imaging by interrogation with an attenuated radiation.

14. The method of claim 1, wherein the administering is achieved through a catheter.

15. A medical device for treating or preventing a vascular condition, comprising

(a) nano-constructs that comprises nanshells, and

(b) delivery means for delivering the nano-construct to a target tissue of a subject,

wherein the nanoshells are capable of absorbing an energy from an electromagnetic radiation or energy from a fluctuating electromagnetic field and translating the energy into heat.

16. The medical device of claim 15, wherein the delivery means is a stent.

17. The medical device of claim 16, wherein the nano-constructs are embedded within a polymer coating on at least a portion of the stent.

18. The medical device of claim 16, wherein the stent comprises a porous structure or micro depots on the surface, and wherein the nano-constructs are placed in the porous structure or the micro depots.

19. The medical device of claim 15, wherein the nano-constructs comprise targeting molecules on the surface of the nano-constructs.

20. The medical device of claim 19, wherein the targeting molecules are surface-conjugated ligands against receptors on an inflamed endothelium.

21. The medical device of claim 15, wherein the energy is a near infrared (NIR) electromagnetic radiation applied through a catheter-based fiber-optic.

22. The medical device of claim 15, wherein the energy is from electromagnetic irradiation applied outside the body of the subject.

23. The medical device of claim 15, wherein the nano-constructs comprise a surface-stealthing compound on the surface of the nano-constructs such that the circulation time of the nano-constructs is increased.

24. The medical device of claim 23, wherein the surface-stealthing compound is poly(ethylene glycol).

25. The medical device of claim 15, wherein the nanoshell comprises a material selected from a metal, carbon, or a conducting polymer.

26. The medical device of claim 15, wherein the nanoshell comprises gold.

27. The medical device of claim 15, wherein the nanoshell has a thickness in the range between about 2 nm and about 100 nm.

28. The medical device of claim 15, wherein the means of delivery comprises a catheter.